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CADTH Reimbursement Review

Provisional Funding Algorithm

Unresectable Hepatocellular Carcinoma

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Background

CADTH has reviewed and issued recommendations for drugs that can be used to treat adults with unresectable hepatocellular carcinoma (HCC).

pERC Recommendation for Atezolizumab (Tecentriq) in Combination With Bevacizumab (Avastin)

Based on the 2020 review of atezolizumab (Tecentriq) in combination with bevacizumab (Avastin) for adult patients with unresectable HCC,[1] the CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC), through the CADTH pan-Canadian Oncology Drug Review (pCODR), issued the following reimbursement recommendation:

- pERC conditionally recommends the reimbursement of atezolizumab in combination with bevacizumab for the first-line treatment of adult patients with unresectable or metastatic HCC who require systemic therapy if the following condition is met: Cost-effectiveness is improved to an acceptable level.

pERC Recommendation for Lenvatinib (Lenvima)

Based on the 2019 review of lenvatinib (Lenvima) for the treatment of unresectable HCC,[2] pERC, through pCODR, issued the following reimbursement recommendation:

- pERC conditionally recommends the reimbursement of lenvatinib (Lenvima) for the first-line treatment of adult patients with unresectable HCC only if the following condition is met: The public drug plan cost of treatment with lenvatinib should not exceed the public drug plan cost of treatment with sorafenib.

pERC Recommendation for Regorafenib (Stivarga)

Based on the 2018 review of regorafenib (Stivarga) for the treatment of unresectable HCC,[3] pERC, through pCODR, issued the following reimbursement recommendation:

- pERC conditionally recommends the reimbursement of regorafenib (Stivarga) for patients with unresectable HCC who have been previously treated with sorafenib only if the following condition is met: Cost-effectiveness is improved to an acceptable level.

pERC Recommendation for Cabozantinib (Cabometyx)

Based on the 2020 review of cabozantinib (Cabometyx) for the treatment of HCC in adults,[4] pERC, through pCODR, issued the following reimbursement recommendation:

- pERC conditionally recommends the reimbursement of cabozantinib (Cabometyx) in adult patients with unresectable HCC in the second-line setting after progression on sorafenib or lenvatinib if the following condition is met: cost-effectiveness is improved to an acceptable level.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of Canadian clinical experts to provide advice for addressing the outstanding implementation issues as follows:

- use of atezolizumab-bevacizumab, sorafenib, and lenvatinib as alternative first-line therapies
- sequencing of currently available tyrosine kinase inhibitors (TKIs) following first-line atezolizumab-bevacizumab.

Consultation Process and Objectives

The implementation advice panel comprised 6 Canadian specialists with expertise in the diagnosis and management of patients with HCC, a representative from a public drug program, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders, including patient and clinician groups, pharmaceutical manufacturers, and public drug programs, were invited to provide input in advance of the meeting.

The advice presented in this report is not necessarily evidence-based but has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice
Use of atezolizumab-bevacizumab, sorafenib, and lenvatinib as alternative first-line therapies	The panel advises that the best available therapy for which the patient is eligible and can tolerate should be used in the first line. Atezolizumab-bevacizumab would be the first-line treatment of choice for eligible patients as it has demonstrated superior overall and progression-free survival outcomes. For patients not eligible for first-line immunotherapy with atezolizumab-bevacizumab, lenvatinib would be available as an alternative first-line treatment, with sorafenib being an option in cases of lenvatinib intolerance or contraindication.
Sequencing of currently available TKIs following first-line atezolizumab-bevacizumab	For patients experiencing disease progression following first-line therapy with atezolizumab-bevacizumab, the panel advises that lenvatinib or sorafenib would offer appropriate second-line options. Emerging evidence suggests that lenvatinib and sorafenib offer efficacy and manageable toxicities for these patients. The panel did not identify any evidence regarding the use of TKIs in subsequent lines (third line and beyond, after atezolizumab-bevacizumab) and thus cannot advise on the use of drugs in this setting.

TKI = tyrosine kinase inhibitor.

In addition to the preceding advice, the panel indicated that all reimbursement recommendations were contingent upon ensuring improved cost-effectiveness so that the relevant treatments are affordable to public payers.

Panel Discussion

Alternative First-Line Therapies

The issue of incorporating atezolizumab-bevacizumab as an alternative first-line therapy in the funding algorithm for patients with unresectable or metastatic HCC was raised with the panel. Current first-line therapies are lenvatinib and sorafenib. There was agreement from the panel that atezolizumab-bevacizumab would be the first-line treatment of choice for eligible patients even if that meant limiting or eliminating subsequent funding options for patients with disease progression. For patients with unresectable HCC who have not received prior systemic therapy, atezolizumab combined with bevacizumab offers superior overall and progression-free survival to sorafenib.[5] The panel stressed that the best available therapy be prioritized as first-line treatment. The panel also agreed that patients who are not suitable candidates for atezolizumab-bevacizumab therapy should have access to lenvatinib or sorafenib as alternative first-line treatments. It was noted that lenvatinib is preferable to sorafenib as it is considered to have less toxicity; however, this is already reflected in current algorithms of most provinces.

Sequential Use of TKIs After Atezolizumab-Bevacizumab

The panel noted that treatment options for patients with HCC who have already received systemic treatment and require subsequent anticancer therapy consist of available TKIs. The panel suggested that patients who received first-line atezolizumab-bevacizumab therapy would be eligible for lenvatinib or sorafenib as second-line therapy. Patients who received lenvatinib or sorafenib as first-line therapy would be eligible for regorafenib or cabozantinib as second-line therapy as per the current funding algorithm. The panel acknowledged that provinces do not currently fund third-line TKIs and that no implementation issue was raised for this setting. As a result, the panel cannot provide further advice on the use of TKIs after two prior TKI therapies.

The panel was confident that sorafenib and lenvatinib will maintain anticancer activity following immunotherapy as has been observed in preliminary clinical evidence.[6] Moreover, this evidence suggests that there are no novel safety concerns when atezolizumab-bevacizumab therapy is followed by TKI therapy.[6] Follow-up of the IMbrave150 trial participants found that 30% of patients treated with atezolizumab-bevacizumab proceeded to receive second-line therapies.[7] This was consistent with the experience of the panel in that a limited number of patients would receive second-line therapy and an even smaller pool of patients would be eligible for third-line therapy in this setting. The panel agreed that third-line TKI treatment options following immunotherapy are currently unsupported by any evidence; therefore, there is considerable uncertainty regarding the clinical and cost-effectiveness of third-line treatment options. Given these limitations, the panel did not feel that funding of third-line therapies for those treated with first-line atezolizumab-bevacizumab would be advised at this time. Despite limiting the number of available subsequent TKI lines of therapy in cases of disease progression in this funding algorithm, atezolizumab-bevacizumab remains the first-line treatment of choice of the panel. There was some consensus that it is unlikely that high-quality evidence will emerge on TKI sequencing subsequent to immunotherapy. However, forthcoming follow-up data from IMbrave150 trial participants[5] and other sources may provide observational evidence regarding the safety

and efficacy of treatment with TKIs following first-line treatment with atezolizumab-bevacizumab.

Provisional Funding Algorithm

Figure 1 depicts the provisional funding algorithm as proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

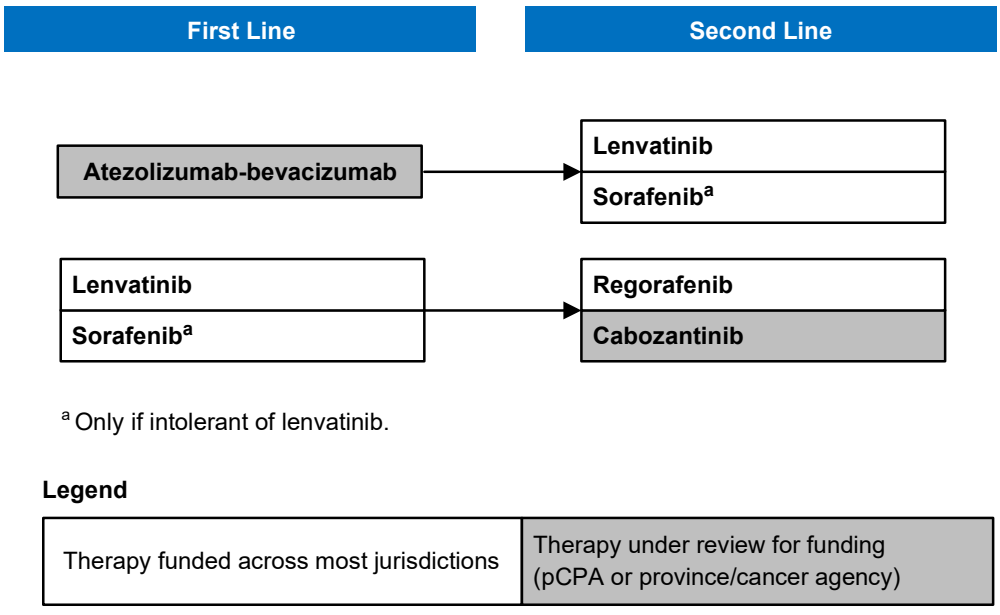
First-Line Setting

For adult patients with previously untreated, unresectable HCC, a choice between atezolizumab-bevacizumab and TKIs is available, with the former being preferred and contingent on provincial funding. Should immunotherapy be unavailable or not indicated for the patient, lenvatinib would be an alternative first-line treatment. In cases of lenvatinib intolerance or contraindication, sorafenib treatment can be offered.

Relapsed or Refractory

Patients who experience disease progression following first-line atezolizumab-bevacizumab therapy may be able to access lenvatinib or sorafenib as second-line therapies, the latter being restricted to lenvatinib intolerance or contraindication. Patients who progress following first-line TKI therapy are eligible to access second-line TKIs (i.e., regorafenib or cabozantinib), where funding is available. Third-line therapies are not funded.

Figure 1: Provisional Funding Algorithm Diagram for Unresectable HCC



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